Genome-wide Linkage Analysis for Aggressive Prostate Cancer in Utah High Risk Pedigrees

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Background

Research has consistently shown that genetics plays a critical role in prostate cancer (CaP) development, but the identification of CaP genes has proven to be very difficult. Hereditary prostate cancer is a complex disease involving numerous genes and variable phenotypic expression. This heterogeneity has led researchers to pursue genes associated with alternative phenotypes for CaP, such as tumor aggressiveness. Several recent linkage studies have used clinical and pathological data to define CaP aggressiveness as a qualitative trait. The International Consortium for Prostate Cancer Genetics (ICPCG) recently completed such an analysis using pooled data from 11 member institutions. This analysis required all families be small to moderate in size in order to facilitate standard linkage analysis software. Hence, although the ICPCG analysis included data from the Utah prostate cancer pedigree resource, the Utah pedigrees were not analyzed in their complete form. Specifically, pedigrees were divided and trimmed before analysis, which reduced the power of the analysis to detect predisposition loci. Here we present the results of a genome-wide scan for aggressive prostate cancer predisposition loci utilizing the full Utah pedigrees.

Materials and Methods

Prostate cancer cases were required to meet at least one of the following criteria in order to be classified as aggressive: 1) regional or distant stage; 2) poorly differentiated or undifferentiated grade; or 3) death due to metastatic prostate cancer, confirmed by death certificate. Any prostate cancer cases not meeting this criteria were classified as having unknown prostate aggressiveness status. We identified 259 subjects with aggressive prostate cancer (APC) in 57 extended and nuclear families. All pedigrees consisted of between two and six generations, with a median of 3 generations. Table I summarizes the characteristics of the pedigrees analyzed.

Table I: Summary of 57 Utah pedigrees with 2 or more aggressive prostate cancer cases

		Per Pedigree		
	Total	Mean	Min	Max
Aggressive CaP cases (APC)	259	4.5	2	20
APC mean age at diagnosis	70.8	70.0	56.5	79.7
APC subjects genotyped	136	2.39	0	12
Other genotyped*	733	12.86	1	56

* connecting ancestors of cases, and spouse with up to four children were genotyped when necessary to infer genotypes

Genotyping was performed by the Center for Inherited Disease Research (CIDR) on a set of 401 STR markers with an average spacing of 9 cM across the 22 autosomes and the X chromosome. Parametric and non-parametric multipoint linkage statistics were calculated using the MCLINK software package, which uses Markov Chain Monte Carlo simulation methods to sample haplotype configurations and to calculate an estimate of the LOD statistic.

Results—Parametric Analysis

No significant results were observed at the genome-wide level, but suggestive evidence for linkage was observed on chromosomes 9q (HLOD=2.04), 14q (HLOD=2.08), and 6p (HLOD=1.75); several pedigrees showed individual evidence for linkage at each locus (LOD > 0.58). Stratification analyses by the number of affected subjects (less than five, five or more) and the average age at diagnosis of affected subjects (less than 70 years, 70 or more years) were also performed. The subset of pedigrees with earlier age at onset demonstrated suggestive linkage evidence on chromosomes 3q (HLOD=1.79), 8q (HLOD=1.67) and 20q (HLOD=1.82). The late onset subset showed suggestive linkage on chromosome 6p (HLOD=2.37) and the subset of pedigrees with fewer than 5 affected subjects showed suggestive linkage on chromosome 10p (HLOD=1.99).

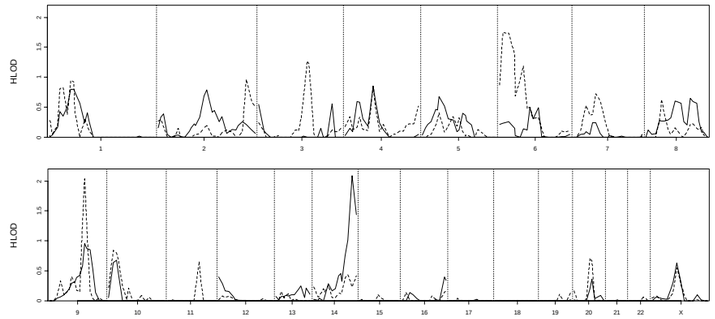

Figure 1: HLOD statistic for chromosomes 1-22 and X. The solid line represents the dominant model, and the broken line represents the recessive model.

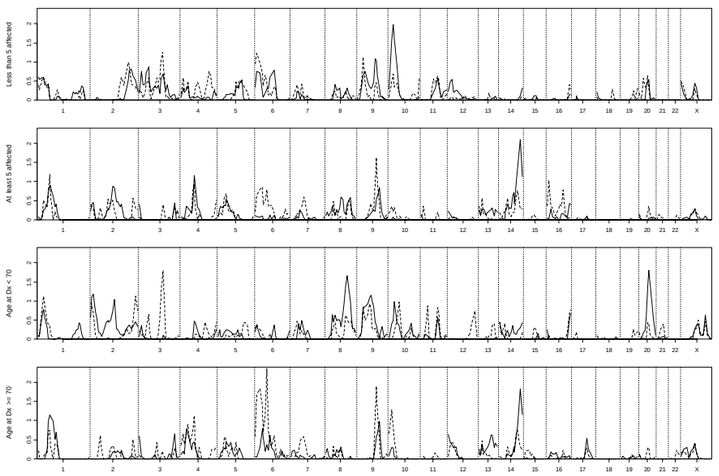

Figure 2: Genome-wide HLOD results for the subsets of pedigrees with less than 5 affected members, 5 or more affected members, average age at diagnosis less than 70 years, and average age at diagnosis equal to or greater than 70 years. The solid line represents results of the dominant model and the broken line represents the recessive model in each frame.

Results—Non-parametric Analysis

Figure 3 shows the qualitative NPL statistic for the 22 autosomes. No significant linkage evidence was observed. The highest NPL statistic observed across the entire genome was 2.33 at D1S255 (56 cM) on chromosome 1p, corresponding to a LOD = 1.45.

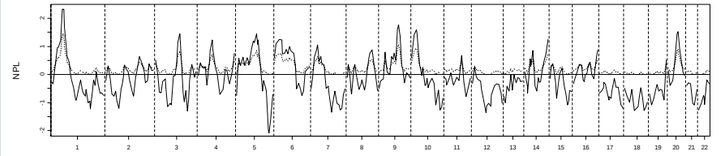

Figure 3: Qualitative NPL statistic for chromosomes 1-22. The solid line represents the NPL statistic, while the broken line shows the equivalent LOD value.

Conclusion

Although this analysis did not identify any regions with significant linkage evidence at the genome-wide level, regions of interest were identified on chromosomes 9, 14, 6, and 1. The result on chromosome 6 appears to support linkage evidence reported previously by the ICPCG as well as the University of Michigan and the ACTANE consortium. Additionally, using pedigree subsets of the data resource identified regions of interest on chromosomes 3, 8, 10 and 20. The chromosome 20 result supports previous findings reported by researchers at Mayo Clinic and the ICPCG. We did not find sufficient evidence to support linkage regions previously reported for aggressive prostate cancer by the ICPCG for chromosome 11, by the University of Michigan for chromosome 15, or by Wake Forest University or Fred Hutchinson for Chromosome 22. Further research is necessary to identify the gene or genes responsible for prostate cancer aggressiveness and surmount the overarching problem of PC heterogeneity.

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